

## Results of bronchial challenge after infantile obstructive bronchitis

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The bronchial hyperreactivity was examined in a follow-up of 206 children having had obstructive bronchitis before two years of age. The acetylcholine challenge was done with 0.5% and 1% Pharmalgen solutions. The bronchial hyperreactivity was established over a 20% decrease of PEF and/or FEV<sub>1</sub> values. Summarizing the results produced by 0.5% and 1% solutions a significant difference could be found in the bronchial hyperreactivity between the follow-up and control groups. Similarly the PC<sub>20</sub> (provocative concentrations) values were suitable for differentiating the two groups. Upon physical exercise, EIB occurred in 2%. With the skin prick test (SPT) by 10 allergens 3+ or 4+ positivity was found in 17% of the children. Between the bronchial hyperreactivity and SPT positivity a significant correlation could be established.

The asthmatic patients have over-sensitive airways [10] and this sensitivity - bronchial hyperreactivity - can be produced by different stimuli: acetylcholine, metacholine, histamine, cold air, potassium chloride, various kinds of exercises, etc. Healthy persons also react upon these stimuli, but the asthmatics do it 100-1000 times more sensitively [26]. Bronchial hyperreactivity after acetylcholine challenge can be detected in 90% of asthmatic subjects [4, 22].

In the course of aspecific bronchial challenges the above mentioned chemicals are given generally for definite periods of time or with a determined breath number in increasing concentrations. Afterwards, one of the lung function parameters detecting the bronchial reaction is measured in

several given intervals. The most frequently used parameter is the FEV<sub>1</sub> value (forced expiratory volume in the first second) at which positivity - bronchial hyperreactivity - is established in a decrease over 20% of the initial value [2, 3, 4, 5, 20]. For the detection of bronchial hyperreactivity after physical exercise (EIB) the free running is generally used which causes the most expressive reaction. Other physical tests in practice are: tread-mill, step-test, jumping and bicycle-ergometer [15, 16, 17, 18, 19].

In the first two years of life 10% of the children undergo an attack of obstructive bronchitis [1] whose clinical picture is known to be similar to the asthma. The verification of bronchial hyperreactivity in this age group



raises a lot of technical difficulties, so in general this problem is approached by follow-up examinations only in older age of life. In the follow-up of children having had obstructive bronchitis in infancy Scislicki et al found bronchial hyperreactivity in 16% by histamine challenge [23], Póder et al by acetylcholine and histamine challenge in 33% [21] and König et al by physical exercise in 12 out of 18 children [18].

In the course of follow-up examinations performed after infantile bronchiolitis some authors have detected a higher proportion of bronchial hyperreactivity using physical exercise and aspecific challenge [11, 24, 25].

In our work we studied the presence of bronchial hyperreactivity by acetylcholine challenge and physical exercise — free running — during the follow-up of 206 children having had obstructive bronchitis before two years of life.

#### PATIENT MATERIAL

Between 1974–76 367 patients had the diagnosis: obstructive bronchitis and invitation letter was sent them to appear at follow-up. The 367 obstructive bronchitic patients mean a ratio of 3.6% of the whole patient material of our Department. Our follow-up included 206 patients which means a 56% ratio.

The criterion of obstructive bronchitis was: before two years of age wheezing with the signs of respiratory tract infection and prolonged expiration, wheezy and rales. The pulmonary hyperinflation can be detected by percussion and X-ray picture.

Among the 206 children appeared in the follow-up the sex distribution was 2:1 for boys. The mean of age was 11 years (between 9–13 years). So after their clinical treatment at least 7 years have gone.

For the sake of comparison, in addition to the data of the 206 children we collected similar data of 82 healthy children, too, on similar questionnaires. In the acetylcholine challenge, the results of 30 healthy children have been used for comparison challenged earlier in our laboratory. These two control groups have similar distribution in age and sex as our patient material. The control children did not have repeated respiratory or chronic diseases or obstructive bronchitis and did not take any drug regularly.

#### METHODS

The follow-up and control children's own and familial anamnestic data on the basis of case histories and final reports were registered on a questionnaire extended according to the experiences of our earlier follow-up. The clinical examination was followed by skin prick test (SPT) with 10 common Bencard allergens (Dermatophagoides pteronyssinus, dog and cat hair, grass mix, tree mix, flower weed and shrub, ragweed and 3 mould preparations: A<sub>13</sub>, M<sub>10</sub>, M<sub>11</sub>). After 15 minutes the urtica with 3–5 mm diameter was evaluated as 3+ and over this diameter with pseudopodium as 4+ positivity.

The bronchial challenge was carried out by inhalation of 0.5 and 1% solution of acetylcholine in two steps from TUR-USI<sub>50</sub> ultrasound nebulizer (air flow 5 l/min, granule size 0.5–8 μm).

At the beginning of the challenge, after 4–5 breathes we waited whether an early reaction occurs or not and after then the 0.5% acetylcholine solution was inhaled for 3 mins. After the inhalation for 3–5 and 10 minutes, the PEF (peak expiratory flow) and FEV<sub>1</sub> values were measured. A decrease over 20% of the initial values



was considered as sign of bronchial hyper-reactivity, i.e. positive reaction. In the case of negative response, we have performed the second inhalation step with 1% solution for 3 mins. Thereafter the PEF and FEV<sub>1</sub> values were repeatedly measured in the same manner. The challenge was performed only with those children who were symptomfree and had no airway infection in the last four weeks.

The exercise test was done in the garden of our Department, where the children ran for 6 minutes with such intensity that in all cases their pulse rate exceeded 170/min. After the exercise in the 5., 10., and 15. minutes the PEF and FEV<sub>1</sub> values were measured. Exercise induced bronchospasm (EIB) was considered in the case of a decrease over 20% of the initial values.

The mathematical statistical evaluation of data got in the course of follow-up was done by computer. In our examination competent information was given by the statistical characteristics of the single measured parameters. So we determined the basic statistics characterizing the parameters (mean, deviation, median, mini-

mum-maximum values, etc.). The means of single data lines of follow-up and control group were compared using an unpaired Student's t-test. From among the contingency analysis methods the independence analysis of variables was carried out by chi square test. In our examinations the  $p < 0.05$  level was stated as significant.

## RESULTS

The acetylcholine challenge was performed with all the 206 children. Their results after having challenged with 0.5 and 1% solutions are summarized in Table I together with the data of control group children. (In the Table the percentile changes of lung function parameters can be found.)

In the control group with a challenge by 0.5% solution the sum of the mean FEV<sub>1</sub> change and of the double of standard deviation (2SD)

TABLE I  
Percentile changes of PEF and FEV<sub>1</sub> values in acetylcholine challenge

	Patients n = 206		Control n = 30	
	mean	dev.	mean	dev.
0.5% sol.				
PEF %	-10.0	11.1	-6.3	7.6
FEV <sub>1</sub> %	-8.3	12.9	-4.9	7.2
1% sol.				
PEF %	-13.2	9.3	-10.1	9.1
FEV <sub>1</sub> %	-11.6	11.2	-9.3	11.0

TABLE II  
Calculated PC<sub>20</sub> values in acetylcholine challenge

	Patients		Control	
0.5% sol.	n = 206	1.20	n = 30	2.01
1% sol.	n = 175	1.73	n = 30	2.14



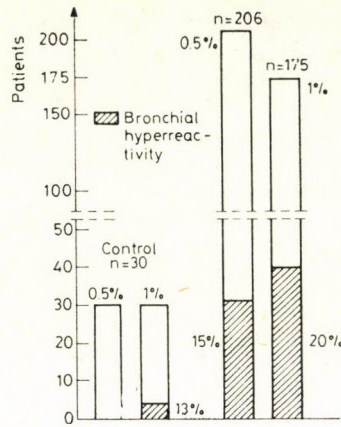


FIG. 1. Frequency of bronchial hyperreactivity in acetylcholine challenge

does not reach 20% (19.3%), accordingly the 20% limit as criterion for the positivity can be accepted also on the basis of our results. In contrast with it the sum of the mean and 2SD of PEF value change has slightly exceeded the 20% limit (21.5%).

On the basis of these criteria from among the 206 children 31 (15%) have shown bronchial hyperreactivity following a challenge with 0.5% solution, while none of the controls did. Upon challenge by 1% solution performed on 175 children—who gave negative response at the first challenge with 0.5% solution—further 40 children (20%) while in controls 4 (13%) produced positive response (see Fig. 1).

To differentiate on the basis of bronchial hyperreactivity the follow-up and control children we calculated the  $PC_{20}$  value for  $FEV_1$  (the calculated acetylcholine concentration at which the 20% decrease of  $FEV_1$  occurs) using the formula of Bronchial Hyperreactivity Working Group (see Table II). On the basis of  $PC_{20}$  values the follow-up group is definitely separated from controls upon 0.5% acetylcholine challenge. The results of acetylcholine challenge of the two groups were analyzed by unpaired t-test. After challenging with 0.5% solution we could not find any significant difference at 5% level between the two groups ( $t = 1.769$ ,

TABLE III

Percentile changes of PEF and  $FEV_1$  values after physical exercise

	Patients		Control	
	mean	dev.	mean	dev.
PEF %	-5.5	6.8	-4.8	7.1
$FEV_1$ %	-6.0	8.1	-5.1	7.6



$t_{\text{table}} = 1.96$ ). The  $t$  value would be significant only at 10% level ( $t_{\text{table}} = 1.644$ ) in the  $FEV_1$  values. In the PEF values and in both PEF and  $FEV_1$  values after 1% solution we could not find any difference between the two groups. Children exhibiting positivity after 0.5% solution will naturally do it after 1% solution of acetylcholine. So if the unpaired  $t$ -test is performed with the results of all finished challenges in the PEF values at 1% ( $t = 2.97$ ,  $t_{\text{table}} = 2.60$ ) and in  $FEV_1$  values at 5% level ( $t = 2.09$ ,  $t_{\text{table}} = 1.97$ ) an unambiguously significant difference can be found between the follow-up and control groups.

The physical exercise was carried out with 204 children, two boys could not participate due to injury. The percental change of PEF and  $FEV_1$  values of the follow-up and control children during exercise is summarized in Table III. EIB was found only in 4 cases while in controls none of the patients produced it. By unpaired  $t$ -test no difference could be detected.

The skin prick test (SPT) showed 3+ or 4+ positivity in 35 children (17%). The most frequent allergens were: cat hair, grass and *D. pteronyssinus*.

The relation of SPT positivity and bronchial hyperreactivity was examined. 28% of SPT positive children (35) and 12% of SPT negative ones (171) had bronchial hyperreactivity after 0.5% solution of acetylcholine. So the SPT positivity and the bronchial hyperreactivity showed significant correlation ( $p < 0.05$ ).

## DISCUSSION

In the follow-up of children having suffered from obstructive bronchitis, bronchial hyperreactivity was found after aspecific challenge in 16–33% [21, 23], while during exercise 2/3 part of the patients developed EIB. In our examination bronchial hyperreactivity in 15% and in 20%, resp. occurred upon acetylcholine challenge with the two kinds of concentrations. On the basis of results got by unpaired  $t$ -test separately after challenging with 0.5% and 1% solutions only a tendency could be observed, but significant difference between the follow-up and control groups could not be stated. Taking into consideration the results of the completed challenges, the unpaired  $t$ -test shows significant difference in both the PEF and  $FEV_1$  values in contrast to the controls. It means that among the follow-up children the bronchial hyperreactivity is more frequent compared to the healthy children, but does not reach that of asthmatics [6, 16].

On the basis of  $PC_{20}$  values the two groups can also be separated, namely the  $PC_{20}$  values of controls are nearly double than those of follow-up children.

In the course of the acetylcholine challenge of healthy children Hopp et al [12, 13] and Götz [14] found bronchial hyperreactivity in 12–15.6%. In our controls upon acetylcholine challenge by 1% solution we have got 15% positivity showing good agreement with the above data.



Upon physical exercise König et al detected EIB in 12 from among 18 children having had obstructive bronchitis [18]. Opposite to this finding in our study only 2% EIB appeared. Kelemen [18] and Kelemen et al [17] found EIB upon various physical exercises only in 51% of the asthmatic children. In their works significant correlation could be shown between EIB and bronchial hyperreactivity after acetylcholine challenge. In our patients having suffered from obstructive bronchitis we did not find such a connection.

It must be remarked that in the above mentioned work of König et al among the 12 children having EIB 7 were asthmatics. It can be supposed that in our follow-up the difference between hyperreactivity upon acetylcholine challenge and EIB is the consequence of higher acetylcholine sensitivity of children having had obstructive bronchitis. Cserháti et al [7] carried out SPT with 20 allergens on healthy children and found 3+ or 4+ positivity in 7%. In the course of the follow-up of obstructive bronchitic children Foucard and Sjöberg [9] detected SPT positivity in 7%, while Scislicki et al in 50% [23]. The 17% positivity of our patients material is higher than that in normals and finds place between the results of the above mentioned two papers.

Summarizing it can be stated that in the course of the follow-up of 206 children without selection having had obstructive bronchitis before two years of age, after acetylcholine challenge bronchial hyperreactivity can be

found in a significantly higher proportion compared to the controls. The SPT positivity is also significantly more frequent among them.

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